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Description

This invention relates to compositions useful as antibacterial agents in humans and other animals. In particular, it relates to liquid suspensions containing macrocrystalline nitrofurantoin.

Nitrofurantoin is an antibacterial agent used extensively in the treatment of urinary tract infections. It is rapidly absorbed in the gastrointestinal tract, and reaches high concentrations in the urine. A general description of nitrofurantoin is found in D. E. Cadwallader, 15 J. American Pharmaceutical Association 409 (1975); and J. D. Conklin, "The Pharmacokinetics of Nitrofurantoin and Its Related Bioavailability," 25 Antibiotics and Chemotherapy 233 (1978).

As with many other pharmaceutical active materials, the pharmacokinetics of nitrofurantoin may be affected by the size and type of nitrofurantoin crystals used in a dosage form. See, for example, J. K. Haleblian, "Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications", 66 J. Pharmaceutical Sciences 1269 (1975). In particular, the use of macrocrystalline nitrofurantoin has been found to reduce the level of emetic side effects that may be associated with nitrofurantoin. This association is discussed in the following articles: H. E. Paul et al., "Laboratory Studies with Nitrofurantoin", 56 J. Pharmaceutical Sciences 882 (1967), and N. Garti et al., "Habit Modifications of Nitrofurantoin Crystallized from Formic Acid Mixtures", 6 Drug Development and Industrial Pharmacy 379 (1980). Macrocrystalline nitrofurantoin having a surface area of from 120 cm^2/g (0.012 M^2/g) to 1000 cm^2/g (0.1 M^2/g) is described in U.S. Patent 3,401,221, Borgmann et al., issued September 10, 1968.

Nitrofurantoin is marketed by Norwich Eaton Pharmaceuticals, Inc., in several dosage forms using nitrofurantoin of differing crystal size. One such dosage form is a suspension of nitrofurantoin monohydrate. The crystals of nitrofurantoin in these suspensions are fine particles typically smaller than 170 mesh. Another solid dosage form contains relatively large crystals of anhydrous nitrofurantoin (from about 40 to about 200 mesh), in a capsule (marketed under the tradename "Macrodantin"). The BET surface area of these macrocrystals is from about 0.06 M^2/g to about 0.15 M^2/g.

A variety of dosage forms of nitrofurantoin are also known in the pharmaceutical literature. For example, solid oral dosage forms of nitrofurantoin are described in U.S. Patent 4,122,157, Huber, issued October 24, 1978; U.S. Patent 4,370,313, Davies, issued January 25, 1983; EP-A-0 250 023, Patel et al., published December 23, 1987; and EP-A-0 250 038, Patel, published December 23, 1987. Suspensions of nitrofurantoin are described in N. Shah et al., "Effect of Polymers on Dissolution from Drug Suspensions", 65 J. Pharmaceutical Sciences 1618 (1976).

None of these references, however, describes an aqueous suspension of macrocrystalline nitrofurantoin. Such a suspension would combine the highly desirable pharmacokinetics of commercially available macrocrystalline nitrofurantoin capsules (Macrodantin), with the benefits of pharmaceutical suspensions. Suspensions may be desirable, for example, for treatment of patients who are unable to swallow capsule or tablet dosage forms. Also, suspensions may facilitate treatment of gastrointestinal disorders, providing rapid and even dispersion of the pharmaceutical active in gastric fluids.

The present invention provides compositions, for the administration of nitrofurantoin to a human or other animal subject, comprising:

(a) a safe and effective amount of nitrofurantoin particulates having a surface consisting of nitrofurantoin monohydrate, wherein said particulates have a mean particle size greater than 200 mesh size;

(b) nitrofurantoin monohydrate;

(c) an effective amount of a suspending agent; and

(d) water;

wherein the pH of said composition is from 1 to 6; and said nitrofurantoin monohydrate is dissolved in said water at saturation level.

The nitrofurantoin of this invention are highly efficacious for the oral delivery of nitrofurantoin. In particular, this invention provides stable, efficacious, aqueous nitrofurantoin suspensions, for the treatment of gastrointestinal disorders and urinary tract infections, without undue side effects.

The attached drawings are photomicrographs of different particulate forms of nitrofurantoin. Specifically:

Figure 1 depicts a perspective view of several nitrofurantoin particulates useful in the compositions of this invention;

Figure 2 depicts a perspective view of several particles of macrocrystalline nitrofurantoin;

Figure 3 depicts a perspective view of several particles of nitrofurantoin monohydrate; and

Figure 4 is a longitudinal sectional view of a portion of a nitrofurantoin particulate useful in the compositions of this invention, comprising approximately 98% nitrofurantoin monohydrate;

A more detailed description of the drawings is set forth in the "Nitrofurantoin" subsection of the description of the invention, below.

These photomicrographs were obtained by mounting the particulates on a Cambridge-type pin stub with double stick tape. (Sectional views were obtained by fracturing the particulates using gentle pressure from a glass coverslip.) The particulates, after mounting, were coated with 200A gold-palladium in a Balzers SCD 040 sputter coater. Examination of the crystals was in a JEOL 840 II scanning electron microscope operated at 20 KV (kilovolts). Images were recorded on a Polaroid P/N 55 film at a magnification of 100 for Figures 1-3, and 300 for Figure 4.

The present invention encompasses certain novel nitrofurantoin dosage forms, useful for administering nitrofurantoin to a human or other animal subject. Specific compounds and compositions to be used in this invention must, accordingly, be pharmaceutically acceptable. As used herein, such a "pharmaceutically-acceptable" component is one that is suitable for use with humans/and or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

The compositions of this invention contain four essential components: nitrofurantoin particulates, nitrofurantoin monohydrate, a suspending agent and water. In particular, these compositions comprise:

(a) a safe and effective amount of nitrofurantoin particulates having a surface consisting of nitrofurantoin monohydrate, wherein said particulates have a mean particle size greater than 200 mesh size;

(b) nitrofurantoin monohydrate;

(c) an effective amount of a suspending agent; and

(d) water;

wherein the pH of said composition is from 1 to 6; and said nitrofurantoin monohydrate is dissolved in said water at saturation level.

Preferably, the nitrofurantoin particulates are present at a level of from 0.1% to 3.5%, more preferably from 0.1% to 1.0%, more preferably from 0.2% to 0.6%. (Unless specified otherwise, all percentages are by total weight of composition.) Also preferably, the pH of the composition is from 2.6 to 6, more preferably from 3.0 to 5.5, more preferably from 3.5 to 5.0.

Nitrofurantoin particulates and nitrofurantoin monohydrate:

"Nitrofurantoin" includes 1-[[(5-nitro-2-furanyl)methylene]-amino]-2,2-imidazolidinedione, and related compounds described in U.S. Patent 2,610,181, Hayes, issued September 9, 1952. Nitrofurantoin is described in the U.S. Pharmacopeia XXI. Nitrofurantoin may be made in a variety of physical forms, including (for example) "nitrofurantoin monohydrate" which contains one mole of water chemically associated with one mole of nitrofurantoin. Nitrofurantoin monohydrate typically occurs in small, needlelike prisms. The crystals are transparent yellow with an adamantine luster. Such crystals are seen in Figure 3 of the drawings. In contrast, "anhydrous nitrofurantoin" contains essentially no chemically-bonded water, and typically occurs in pinacoid prisms with a length: width ratio of 3:1. The crystals are transparent to translucent yellow, with a nonmetallic waxy luster. Such crystals are seen in Figure 2 of the drawings. (Descriptive terms for crystals and particulates, used herein, are discussed in B. Mason and L. Berry, Elements of Mineralogy (1969).

The compositions of this invention contain nitrofurantoin monohydrate "dissolved in said water saturation level", i.e., in solution at the maximum concentration of nitrofurantoin monohydrate possible in the aqueous composition, at ambient conditions. Therefore, the exact amount of nitrofurantoin monohydrate in the present compositions will depend upon the amount of water present, and the pH of the composition. For typical compositions, though, this level is from 0.010% to 0.027%. In preferred compositions, nitrofurantoin monohydrate is present at a level of from 0.01% to 0.018%.

The "nitrofurantoin particulates" of this invention are comprised of discrete particulates of nitrofurantoin, having a surface consisting of nitrofurantoin monohydrate, wherein said particulates are larger than 200 mesh size. Preferably the particulates have a size distribution of from 30 mesh to 100 mesh, more preferably from 40 mesh to 60 mesh. Also preferably, the BET surface area of the particulates is at least about 0.2 M^2/g more preferably at least about 0.4 M^2/g. Preferred nitrofurantoin particulates useful herein are described in U.S. Patent Application Serial No.07/386050, (EP-A- 0 412 592) (Norwich case N-537), Cazer et al., entitled "Nitrofurantoin Crystals", filed July 25 1989.

In the commercial manufacture of nitrofurantoin particulates useful in this invention, the particle size and BET surface area of the particulates may vary somewhat from the ranges described herein. Such commercial materials may have a distribution of values for these parameters, with mean values within the ranges described above.

A "safe and effective amount" of nitrofurantoin particulates is an amount that is effective to inhibit microbial growth at the site of an infection to be treated in a human or lower animal subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with

such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the nitrofurantoin particulates therein, and the dosage regimen desired for the composition.

"Size" of the nitrofurantoin particulates of this invention refers to the measurement of the largest U. S. Standard mesh screen through which substantially all of the particulates will pass. In general, this mesh measurement is a function of the smallest dimension of the particulates being measured. As this minimum dimension of the particulates increases, the mesh size will decrease. For example, as used herein, particulates "larger than 200 mesh size" means that substantially all of the particulates will pass through a U.S. Standard mesh screen of less than 200 mesh, with few particulates passing through the 200 mesh screen. Also, particulates having a size distribution "of from 40 mesh to 60 mesh" (also referred to as "40/60 mesh" particles) means that substantially all of the particulates will pass through a 40 mesh screen, and essentially none of the particles will pass through a 60 mesh screen. Mesh measurements are discussed in "Screening", Chemical Engineer's Handbook, 4th Edition 21-46 (J. Perry, editor).

As referred to herein, "the BET surface area" of nitrofurantoin particulates refers to the measurement of the surface area in immediate contact with an inert gas into which the particulate is placed, measured by the means generally described in S. Brunnaer et al., 60 J. American Chemical Society 309A (1938), using a single point measurement technique on a Micromeritics Flowsorb II 2300 (manufactured by Micromeritics Instrument Corporation, Norcross, Georgia, U.S.A.). The particulate sample is degassed at approximately 140°C (284°F) for approximately 15 minutes. The analysis gas is nitrogen/helium at a molar ratio of 30/70. Cooling baths are liquid nitrogen, and the apparatus is calibrated using nitrogen gas injected with a gas-tight syringe.

Preferred nitrofurantoin particulates useful in this invention have bulk physical characteristics similar to those of macrocrystalline anhydrous nitrofurantoin. In particular, the nitrofurantoin particulates are typically pinacoid prisms with a length:width ratio of about 3:1. These particulates are acicular microcrystalline aggregates with a nonmetallic silky to earthy luster. Several of these nitrofurantoin particulates are depicted in Figure 1. Particulate 1 is a perspective view, showing both a face along its long axis and a face along its short axis. Particulate 2 is a perspective view, showing two faces along the long axis of the particulate. The similarity of the bulk physical characteristics of these particulates to the bulk physical characteristics of macrocrystalline anhydrous nitrofurantoin can be seen by comparison of the particulates depicted in Figure 1 with those depicted in Figure 2.

The surface of the nitrofurantoin particulates preferably consists essentially of nitrofurantoin monohydrate. The "surface" is the portion of the nitrofurantoin particulate that is in immediate contact with a fluid into which the particulate is submersed. The remaining, inner portion of the nitrofurantoin particulate (the "core") is comprised of anhydrous nitrofurantoin, nitrofurantoin monohydrate, or mixtures thereof.

Accordingly, the nitrofurantoin particulates of this invention are preferably comprised of from 5% to 100% of nitrofurantoin monohydrate. More preferably, the nitrofurantoin particulates comprise at least 50%, more preferably at least 90%, nitrofurantoin monohydrate. Nitrofurantoin particulates containing less than 100% nitrofurantoin monohydrate consist of: a "surface layer" comprising nitrofurantoin monohydrate as the monohydrate crystalline forms on the surface, and in the contiguous portion of the core; with the remaining portion (if any) of the core comprising anhydrous nitrofurantoin.

The portion of nitrofurantoin particulates comprised by nitrofurantoin monohydrate and nitrofurantoin anhydrous may be determined using standard analytical techniques well known in the art. In particular, the relative proportion of nitrofurantoin monohydrate in the nitrofurantoin particulates may be determined by thermogravimetric analysis. The chemically-bonded water of the monohydrate is driven off by heating, resulting in a weight loss. This weight loss is a function of the amount of monohydrate in a sample analyzed. Specifically, a thermogravimetric scan is performed on a sample of nitrofurantoin particulates (unground) of from 5 to 10 milligrams, under nitrogen, over the temperature range of from 30°C (86°F) to 220°C (428°F), scanned at a rate of 5°C per minute. The chemically-bound water is measured as the weight loss occurring in the range of from 80°C (176°F) to 150°C (302°F). This lost weight constitutes approximately 7% of the weight of the nitrofurantoin monohydrate originally in the sample. Accordingly, the weight of nitrofurantoin monohydrate in the sample is determined by multiplying the weight of lost water by approximately 14.3. This weight is then compared to the weight of the original sample, to determine the percentage of nitrofurantoin monohydrate in the sample. A general description of such analyses useful herein is set forth in Thermal Analysis, 3d edition (W. Wendlandt, editor, 1986).

The presence of nitrofurantoin monohydrate on the surface of the particulates may be determined by attenuated total reflectance infrared spectroscopy. Samples of particulates are placed on a KRS-5 crystal (having approximately 50 cm x 3 cm x 3 cm dimensions), at a 45 degree entry angle. A 4 cm^{-1} resolution spectrum is obtained over the range of from 4000 cm^{-1} to 450 cm^{-1}. Distinct absorbance is seen at the following wavenumbers (+/- 5): 3618, 3474, 1778, 1723, 1132, 1018, 893, and 877. By comparison, absorbance for anhydrous

nitrofurantoin is seen at the following wavenumbers (+/- 5): 1800, 1775, 1741, 1724, 1104, 1013, 901, and 867. Anhydrous nitrofurantoin will also pass identity test part B for nitrofurantoin, U.S. Pharmacopeia XXI, page 735.

Preferred nitrofurantoin particulates among those useful in this invention may be made by the method comprising the steps of:

(a) preparing a saturated aqueous solution of nitrofurantoin monohydrate;

(b) adding to said solution anhydrous nitrofurantoin having a particle size larger than 200 mesh, at a level of 100 grams per liter of said solution;

(c) mixing said solution for at least 5 minutes; and

(d) filtering said solution.

The anhydrous nitrofurantoin added in step (b) preferably has a particle size distribution of from 30 mesh to 100 mesh, more preferably from 40 mesh to 60 mesh. This particle size is selected to yield the particular particle size desired in the final nitrofurantoin particulate product. Preferably, said solution is mixed in step (c) for at least 6.5 hours.

The anhydrous nitrofurantoin and the saturated nitrofurantoin monohydrate solution are mixed, in step (c), for a period of time sufficient to yield a particulate having a desired nitrofurantoin monohydrate composition. Nitrofurantoin particulates having low levels of nitrofurantoin monohydrate (i .e., about 5%) are prepared by processes wherein this mixing step is about 5 minutes. Nitrofurantoin particulates comprising 100% nitrofurantoin monohydrate are made by processes wherein the mixing step is continued for 24 hours. The specific duration of the mixing step will vary according to such factors as the size and configuration of the mixing vessel, the rate of mixing, and the size and surface characteristics of the nitrofurantoin anhydrous crystals used (the effective surface area of nitrofurantoin anhydrous exposed to the saturated solution of nitrofurantoin monohydrate). The specific mixing time to yield a nitrofurantoin particulate having a specific composition of nitrofurantoin monohydrate may be determined by routine experimentation.

Suspension Agent:

The compositions of this invention employ a suspension system comprising one or more compounds (herein "a suspension agent") that maintain the nitrofurantoin particulates in an essentially uniform aqueous suspension at typical conditions of storage and use. Such suspension systems, suspension agents, and methods of their use include those well known in the art. See, for example, M. Pernarowski, "Solutions, Emulsions and Suspensions", Remington's Pharmaceutical Sciences (A. Osol, editor, 15th Edition, 1975). Suspension agents useful in the compositions of this invention include, for example, cellulose ethers (such as methylcellulose, hydroxyethylcellulose, and carboxymethylcellulose), alginates, carboxyvinylpolymers, xanthan gum, colloidal silicas, montmorillonite clays and hydrophobically treated montmorillonite clays (such as magnesium aluminum silicate), and mixtures thereof. Preferred suspension agents include mixtures of cellulose ethers and magnesium aluminum silicate.

One preferred suspension system employs a mixture of methylcellulose and magnesium aluminum silicate. In such a system, methylcellulose may be used at levels of from 0.1% to 10%, preferably from 0.5% to 1.5%, and magnesium aluminum silicate may be used at levels of from 0.19% to 10%, preferably from 2.5% to 4.0%. Methylcellulose, or cellulose methyl ether, is commercially available from a variety of sources as a chemically treated plant cellulose derivative. Among such methylcellulose materials useful herein is Methocel, sold by Dow Chemical Company. Magnesium aluminum silicate (or aluminum magnesium silicate) is of the formula $Al_2MgO_8Si_2$, occurring naturally in such smectite minerals as colerainite, saponite, and sapphirine. Refined magnesium aluminum silicates useful herein are readily available, such as Veegum, manufactured by R. T. Vanderbilt Company, Inc.

Optional Components:

The compositions of the present invention may also contain optional components that modify the physical characteristics and/or therapeutic effects of the compositions. Such optional components must not, however, substantially affect, in an adverse manner, the therapeutic activity of the nitrofurantoin particulates. The optional components useful herein must not also substantially affect, in an undesired manner, the viscosity of the aqueous suspension. Preferred optional components useful herein include colorants, sweeteners, and flavorants, typically at levels of from 0.01% to 0.2%. A dispersant material, such as glycerin, is a preferred optional ingredient, present at a level of from 5% to 40%, preferably from 10% to 20%.

The compositions of this invention preferably contain an "antiseptic agent", i.e., one or more materials that prevent or arrest the growth or action of microorganisms by inhibiting their activity and/or by destroying them. These materials are preferably present at a level of from 0.001% to 0.5%. Many antiseptic materials are known

in the art, including preservatives, disinfectants and antiseptics. Such materials are described, for example, in Disinfection, Sterilization and Preservation 3d (S. Block ed., 1983).

The pH of the present compositions may be adjusted by addition of a pharmaceutically-acceptable acid or base. Suitable acids include, for example, hydrochloric acid and carboxylic acids such as citric acid, tartaric acid and succinic acid. Suitable bases include, for example, the oxides and hydroxides of calcium, potassium, sodium and magnesium, alkaline quaternary compounds, alkaline amino acids, and mixture thereof.

The compositions of this invention may be made by any of a variety of processes well known in the industry. Such processes typically involve admixture of the components, followed by homogenizing. As will be appreciated by those skilled in the art, the conditions under which the compositions are mixed and homogenized may have an effect on the product viscosity.

An infectious disorder in a human or other animal subject, can be treated a prevented, by administering a safe and effective amount of a nitrofurantoin suspension of this invention, to said subject. As used herein, an "infectious disorder" is any disorder characterized by the presence of a microbial infection. The composition according to this invention is preferably used for the treatment of bacterial infections, particularly for genitourinary infections, and gastrointestinal infections.

The specific dosage of nitrofurantoin to be administered, as well as the duration of treatment, are mutually dependent. The dosage and treatment regimen will also depend upon such factors as the type of dosage form used, the infectious agent present, the ability of the nitrofurantoin particulates to reach sustained effective levels at the site of the infection, the nature and extent of other infections (if any), the personal attributes of the subject (such as weight), compliance with the treatment regimen, and the presence and severity of any side effects of the treatments.

Typically, for a human adult (weighing approximately 70 kilograms), from 1 mg to 1,000 mg, more preferably from 10 mg to 400 mg, more preferably from 20 mg to 200 mg, of nitrofurantoin particulates are administered per day. Treatment regimens preferably extend from 3 to 56 days, preferably from 7 to 28 days in duration.

The composition of the present invention is preferrably used for the treatment and prophylaxis of upper-gastrointestinal disorders mediated by Campylobacter pylori. (see EP-A-0219 912, Kraft et al., published April 29, 1987) Nitrofurantoin particulates according to the present invention for the treatment of a human or other animal subject having such upper-gastrointestinal disorders are administered to said subject at a level of from 10 mg to 400 mg per day, for from 3 to 60 days.

EXAMPLE I

Nitrofurantoin particulates for use in this invention are made by adding approximately 200 g (grams) of nitrofurantoin monohydrate to approximately 40 L (liters) of deionized water, in a suitable container. This mixture is stirred for approximately 30 minutes, at ambient temperature (approximately 68°F, 20°C). The mixture is then filtered, removing the undissolved nitrofurantoin monohydrate.

Approximately 4 kg (kilograms) of 40/60 mesh screened anhydrous nitrofurantoin macrocrystals are then added to the saturated nitrofurantoin monohydrate solution. This mixture is then stirred for approximately 6.5 hours, at ambient temperature.

The mixture is then filtered, and the nitrofurantoin particulates washed with ether. The particulates are then air dried for approximately 1 hour. The particulates are further dried for approximately 24 hours at 60°C (140°F).

Thermal gravimetric analysis of the particulates indicates that the particulates are comprised of approximately 98% nitrofurantoin monohydrate. The particles are screened, and are found to have a size of from 40 to 60 mesh. The BET surface area is measured to be approximately 5.8 M^2/g. An attenuated reflectance infrared spectrum is performed, and distinct absorbance is seen at the wavenumbers characteristic of nitrofurantoin monohydrate.

A composition of this invention is then made having the following composition:

Component	% (by weight)
nitrofurantoin particulates	0.508
nitrofurantoin monohydrate	0.018
magnesium aluminum silicate	3.010
sodium carboxymethylcellulose	1.180
glycerin	13.570
sorbitol	15.050
methyl paraben®	0.129
propyl paraben®	0.022
citric acid	0.726
purified water	65.787

The magnesium aluminum silicate is added to approximately one third of the water, and mixed for approximately one hour, at approximately 50°C (122°F). Separately, the glycerin, methyl paraben, propyl paraben, and carboxymethylcellulose are mixed. This mixture is then slowly added to the magnesium aluminum silicate/water mixture. The sorbitol, citric acid and remaining water is added, and the mixture stirred for approximately 1.5 hours.

The nitrofurantoin monohydrate is then added to the solution, and mixed for approximately 2 hours. The nitrofurantoin particulates are added, and the mixture stirred for approximately 3 hours.

A human subject suffering from gastritis mediated by Campylobacter pylori is administered approximately 20 ml of this suspension (approximately 100 mg of nitrofurantoin), 4 times a day, for 28 days. Stomach cultures of the subject indicate the organism has been eradicated, with corresponding improvement in the subject's symptoms.

EXAMPLE II

A composition according to this invention is made comprised as follows.

Component	% (by weight)
nitrofurantoin particulates*	0.53
nitrofurantoin monohydrate	0.02
magnesium aluminum silicate	1.20
pectin	1.11
glycerin	20.18
methyl paraben®	0.12
propyl paraben®	0.02
purified water	76.82

*: made according to the method described in Example I

The composition is made by dissolving the methyl paraben and propyl paraben in a portion of the water, followed by the magnesium aluminum silicate, to form a "bulk mixture". The bulk mixture is then stirred for approximately 1 hour. The pectin is then added to approximately one-half of the glycerin, mixed for approximately 1 hour, and added to the bulk mixture. The nitrofurantoin monohydrate is then added. Separately, the nitrofurantoin particulates are added to the remaining portion of glycerin. This mixture is finally added to the bulk mix-

ture, and the final composition stirred for approximately 1 hour.

A human subject suffering from a urinary tract infection caused by Escherichia coli is administered approximately 20 ml of this suspension (approximately 100 mg of nitrofurantoin), 4 times a day, for 10 days. The infection is thereby eradicated.

EXAMPLE III

A composition according to this invention is made comprised as follows:

Component	% (by weight)
nitrofurantoin particulates*	1.000
nitrofurantoin monohydrate	0.025
magnesium aluminum silicate	0.500
xanthan gum	0.600
flavorants	0.080
methyl paraben®	0.120
propyl paraben®	0.020
purified water	97.655

*: made according to the method described in Example I

The composition is made by dissolving the methyl paraben, propyl paraben, and flavorants in a portion of the water, followed by the magnesium aluminum silicate, to form a "bulk mixture". The bulk mixture is then stirred for approximately 1 hour. The xanthan gum then added to the bulk mixture, and stirred for approximately 20 minutes. The nitrofurantoin monohydrate is then added. The nitrofurantoin particulates are then added, and the final composition stirred for approximately 1 hour.

A human subject suffering from a urinary tract infection is administered approximately 20 ml of this suspension (approximately 200 mg of nitrofurantoin), 2 times a day, for 10 days. The infection is thereby eradicated.

Claims

1. A composition, for the administration of nitrofurantoin to a human or other animal subject, comprising:
   (a) a safe and effective amount of nitrofurantoin particulates having a surface consisting of nitrofurantoin monohydrate, wherein said particulates have a mean particle size greater than 200 mesh size;
   (b) nitrofurantoin monohydrate;
   (c) an effective amount of a suspending agent; and
   (d) water;
   wherein the pH of said composition is from 1 to 6; and said nitrofurantoin monohydrate is dissolved in said water at saturation level.

2. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 1, wherein said pH is from 3.5 to 5.0.

3. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 2, wherein said nitrofurantoin monohydrate is present at a level of from 0.010% to 0.027%.

4. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 1, wherein said nitrofurantoin particulates are present at a level of from 0.1% to 3.5%.

5. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to

Claim 4, wherein said nitrofurantoin particulates have a BET surface area of at least about 0.2 M^2/g.

6. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 5, wherein said nitrofurantoin particulates have a size distribution of from 40 mesh to 60 mesh.

7. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 6, wherein said nitrofurantoin particulates are made by a process comprising the steps of:
(a) preparing a saturated aqueous solution of nitrofurantoin monohydrate;
(b) adding to said solution anhydrous nitrofurantoin having a particle size larger than 200 mesh;
(c) mixing said solution for at least 5 minutes; and
(d) filtering said solution.

8. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 7, wherein said solution is mixed in said step (c) for at least 6.5 hours.

9. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 6, wherein said suspension agent comprises methyl cellulose and magnesium aluminum silicate.

10. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 9, wherein said methyl cellulose is present at a level of from 0.5% to 1.5%, and said magnesium aluminum silicate is present at a level of from 2.5% to 4%.

11. A composition, for the administration of nitrofurantoin to a human or other animal subject, comprising:
(a) from 0.1% to 3.5% of nitrofurantoin particulates having a surface consisting of nitrofurantoin monohydrate, wherein said particulates have a mean particle size distribution of from 30 mesh to 100 mesh and a BET surface area of at least about 0.2 M^2/g;
(b) nitrofurantoin monohydrate;
(c) methyl cellulose at a level of from 0.1% to 10%;
(d) magnesium aluminum silicate a a level of from 0.2% to 10%; and
(e) water;
wherein the pH of said composition is from 3 to 5.5; and said nitrofurantoin monohydrate is dissolved in said water at saturation level.

12. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 11, wherein said nitrofurantoin particulates are present at a level of from 0.2% to 0.6%, and said BET surface area is at least about 0.4 M^2/g.

13. A composition, for the administration of nitrofurantoin to a human or other animal subject, according to Claim 12, wherein said methyl cellulose is present at a level of from 0.5% to 1.5%, and said magnesium aluminum silicate is present at a level of from 2.5% to 4%.

Patentansprüche

1. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt,welche enhält:
(a) eine sichere und wirksame Menge von teilchenförmigem Nitrofurantoin, welches eine aus Nitrofurantoinmonohydrat bestehende Oberfläche aufweist, wobei dieses teilchenförmige Nitrofurantoin eine mittlere Teilchengröße größer als 200 mesh aufweist;
(b) Nitrofurantoinmonohydrat;
(c) eine wirksame Menge eines Suspendiermittels; und
(d) Wasser;
wobei der pH-Wert dieser Zusammensetzung 1 bis 6 beträgt; und wobei das Nitrofurantoinmonohydrat in dem Wasser in einer der Sättigung entsprechenden Menge aufgelöst ist.

2. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 1, deren pH-Wert 3,5 bis 5,0 beträgt.

3. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tie-

risches Subjekt nach Anspruch 2, wobei das Nitrofurantoinmonohydrat in einer Menge von 0,010 bis 0,027 % vorliegt.

4. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 1, wobei das teilchenförmige Nitrofurantoin in einer Menge von 0,1 % bis 3,5 % vorliegt.

5. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 4, worin das teilchenförmige Nitrofurantoin eine BET-Oberfläche von wenigstens etwa 0,2 m^2/g aufweist.

6. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 5, worin das teilchenförmige Nitrofurantoin eine Teilchengrößenverteilung von 40 bis 60 mesh aufweist.

7. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 6, wobei das teilchenförmige Nitrofurantoin nach einem Verfahren hergestellt wird, welches die folgenden Stufen umfaßt:
(a) Herstellen einer gesättigten wässerigen Lösung von Nitrofurantoinmonohydrat;
(b) Hinzufügen von wasserfreiem Nitrofurantoin mit einer Teilchengröße größe als 200 mesh zu dieser Lösung;
(c) Vermischen dieser Lösung während wenigstens 5 min; und
(d) Filtrieren dieser Lösung.

8. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 7, wobei die Lösung in der Stufe (c) während wenigstens 6,5 h vermischt wird.

9. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 6, wobei das Suspendiermittel Methylzellulose und Magnesiumaluminiumsilikat umfaßt.

10. Zusammensetzung zur Verabreichung Von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 9, wobei die Methylzellulose in einer Menge von 0,5 % bis 1,5 % vorliegt und wobei das Magnesiumaluminiumsilikat in einer Menge von 2,5 % bis 4 % vorliegt.

11. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt, welche enthält:
(a) 0,1 % bis 3,5 % des teilchenförmigen Nitrofurantoins, welches eine aus Nitrofurantoinmonohydrat bestehende Oberfläche aufweist, wobei dieses teilchenförmige Nitrofurantoin eine Verteilung der mittleren Teilchengrößen von 30 bis 100 mesh und eine BET-Oberfläche von wenigstens etwa 0,2 m^2/g aufweist;
(b) Nitrofurantoinmonohydrat;
(c) Methylzellulose in einer Menge von 0,1 % bis 10 %;
(d) Magnesiumaluminiumsilikat in einer Menge von 0,2 % bis 10 %; und
(d) Wasser;
wobei der pH-Wert der Zusammensetzung 3 bis 5,5 beträgt; und wobei das Nitrofurantoinmonohydrat in dem Wasser in einer der Sättigung entsprechenden Menge gelöst ist.

12. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 11, wobei das teilchenförmige Nitrofurantoin in einer Menge von 0,2 % bis 0,6 % vorliegt und wobei die BET-Oberfläche wenigstens etwa 0,4 m^2/g beträgt.

13. Zusammensetzung zur Verabreichung von Nitrofurantoin an ein Human-Subjekt oder an ein anderes tierisches Subjekt nach Anspruch 12, wobei die Methylzellulose in einer Menge von 0,5 % bis 1,5 % vorliegt und wobei das Magnesiumaluminiumsilikat in einer Menge von 2,5 % bis 4 % vorliegt.

Revendications

1. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, la composition comprenant :
   (a) une quantité sûre et efficace de particules de nitrofurantoïne ayant une surface consistant en monohydrate de nitrofurantoïne, lesdites particules ayant une taille particulaire moyenne supérieure à l'ouverture de maille correspondant à un tamis n° 200;
   (b) du monohydrate de nitrofurantoïne;
   (c) une quantité efficace d'un agent de mise et maintien en suspension; et
   (d) de l'eau;
   le pH de ladite composition étant de 1 à 6, et ledit monohydrate de nitrofurantoïne étant dissous dans ladite eau à un niveau de saturation.

2. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 1, dans laquelle ledit pH est de 3,5 à 5,0.

3. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 2, dans laquelle ledit monohydrate de nitrofurantoïne est présent en une proportion de 0,010% à 0,027 %.

4. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 1, dans laquelle lesdites particules de nitrofurantoïne sont présentes en une proportion de 0,1 % à 3,,5 %.

5. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 4, dans laquelle lesdites particules de nitrofurantoïne ont une surface spécifique BET au moins égale à environ 0,2 m^2/g.

6. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 5, dans laquelle lesdits particules de nitrofurantoïne ont une distribution de leur taille allant de l'ouverture de maille caractérisant un tamis n 40 à celle caractérisant un tamis n° 60.

7. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 6, dans laquelle lesdites particules de nitrofurantoïne sont obtenues par un procédé comprenant les étapes consistant à :
   (a) préparer une solution aqueuse saturée de monohydrate de nitrofurantoïne;
   (b) ajouter à ladite solution de la nitrofurantoïne anhydre ayant une taille particulaire supérieure à l'ouverture de maille caractérisant un tamis n° 200;
   (c) mélanger cette solution pendant au moins 5 minutes; et
   (d) filtrer ladite solution.

8. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 7, dans le cas de laquelle ladite solution est mélangée dans ladite étape (c) pendant au moins 6 heures et demi.

9. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 6, dans laquelle ledit agent de mise et maintien en suspension comprend de la méthylcellulose et du silicate de magnésium et d'aluminium.

10. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 9, dans laquelle ladite méthylcellulose est présente en une proportion de 0,5 % à 1,5 %, et ledit silicate de magnésium est présent en une proportion de 2,5 % à 4 %.

11. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, comprenant :
   (a) de 0,1 à 3,5 % de particules de nitrofurantoïne ayant une surface consistant en monohydrate de nitrofurantoïne, dans laquelle lesdites particules ont une distribution de leur taille particulaire moyenne allant d'une valeur correspondant à l'ouverture de maille d'un tamis n 30 à celle d'un tamis n° 100 et ayant une surface spécifique BET au moins égale à environ 0,2 m^2/g.

(b) un monohydrate de nitrofurantoïne;
(c) de la méthylcellulose, présente en une proportion de 0,1 % à 10 % ;
(d) du silicate d'aluminium de magnésium présent en une proportion de 0,2 % à 10 %; et
(e) de l'eau;

le pH de ladite composition étant de 3 à 5,5, et ledit monohydrate de nitrofurantoïne étant dissous au niveau de la saturation dans ladite eau.

12. Composition pour l'administration de la nitrofurantoïne à un être humain ou à un autre sujet animal, selon la revendication 11, dans laquelle les particules de nitrofurantoïne sont présentes en une proportion de 0,2 à 0,6 %, et la surface spécifique BET vaut au moins environ 0,4 m^2/g.

13. Composition pour l'administration de la nitrofurantoïne à un être humain ou a un autre sujet animal, selon la revendication 12, dans laquelle la méthylcellulose est présente en une proportion de 0,5 % à 1,5 % et ledit silicate d'aluminium de magnésium est présent en une proportion de 2,5 % à 4 %.

Fig. 1

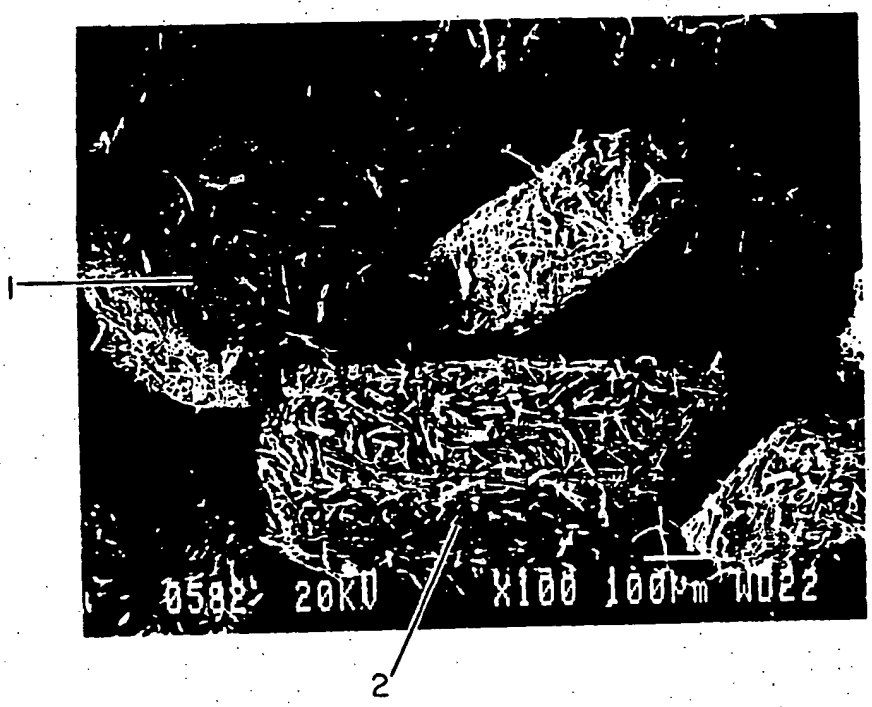
1
2
0582 20KV X100 100µm WD22

Fig. 2

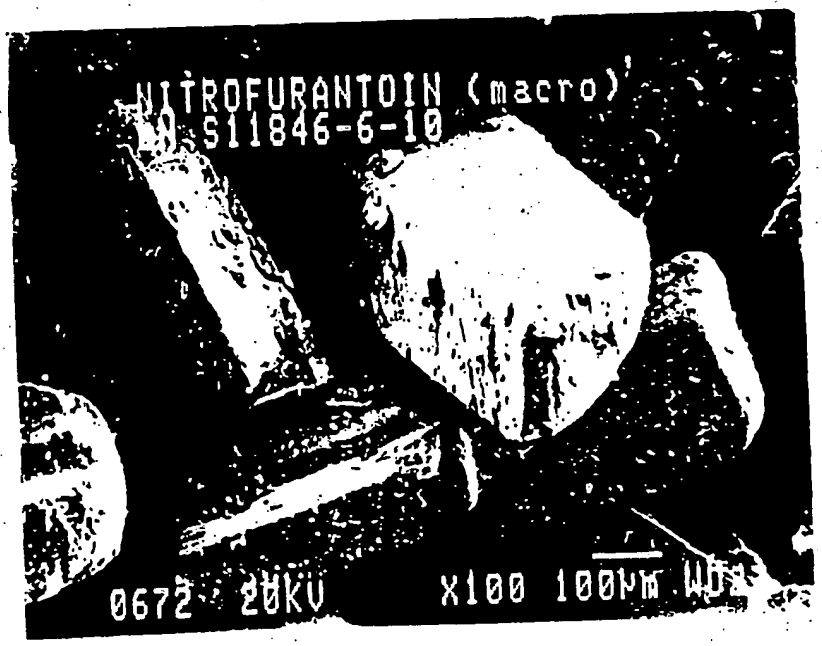
NITROFURANTOIN (macro)
S11846-6-10
0672 20KV X100 100µm

Fig. 3

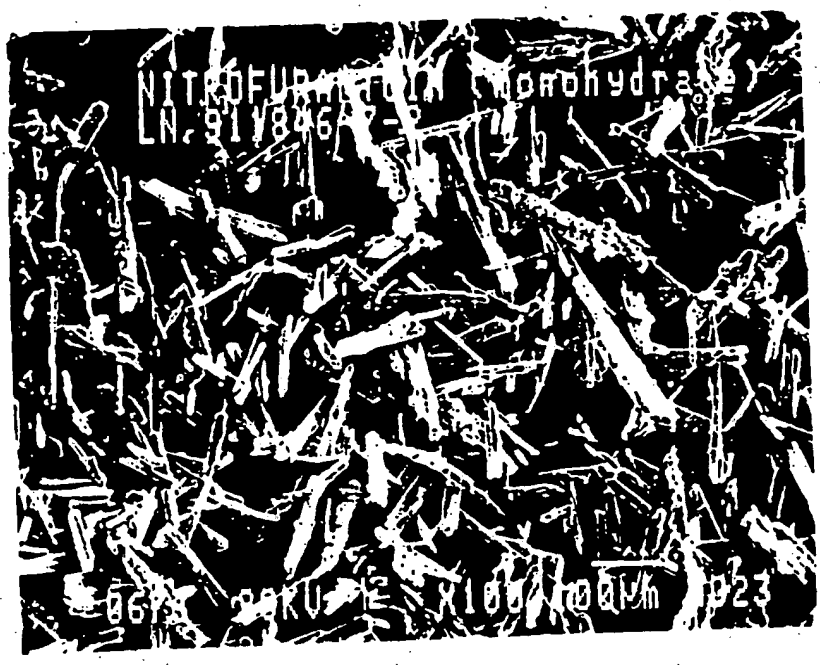

Fig. 4